Relationship of Albumin-CRP Ratio on Neoadjuvan Clinical Response of Caf Regiment Chemotherapy in Women with *Locally Advance Breast Cancer* in Rsud Dr. Soetomo

Lintong Darianto S. Damanik[1], Hantoro Ishardyanto[2]

[1]Resident of Surgery, Faculty of Medicine Universitas Airlangga /Dr. Soetomo General Hospital Surabaya,
[2]Staff of the Department of Surgery, Oncology Division, Faculty of Medicine Universitas Airlangga /Dr. Soetomo General Hospital Surabaya

Abstract

Background : Breast cancer is the most common cancer in women and is the highest cause of death. As many as 2.1 million women in the world suffer from breast cancer each year. Data in Dr. Soetomo Hospital show patient cancer breast came with a case of locally advanced breast cancer as much as 47% and 52% of the cases do not respond well to neoadjuvant chemotherapy. The inflammatory state and nutritional status of the patient play a role in the therapeutic success of the patient. The presence of inflammation and the status of the nutrients are poorly related to the response of clinically against chemotherapy are low. The state of inflammation and status of nutrition it can be seen from the ratio between CRP with albumin.

Method: The research was a prospective cohort design, on patients with locally advanced breast cancer. Patients performed the examination levels of albumin and CRP before the chemotherapy is given and carried out the measurement of the mass of the tumor with a physical examination. Then the patient underwent neoadjuvant chemotherapy with the CAF regimen for 3 cycles and was examined for CRP, albumin, and tumor size again. Then evaluated for response to therapy.

Results: In this study, a total of 35 patients were obtained with 12 people (34.3%) with a low CRP / Albumin ratio and 23 people (65.7%) with a high CRP / Albumin ratio. From the clinical response found 0 people (0%) with progressive disease, 7 people (20%) with stable disease, 23 people (65.7%) with partial response and 5 people (14.3%) with complete response. Statistical test results showed that there was a significant relationship between CRP / Albumin ratio with chemotherapy response ($p = 0.004$).

Conclusion: It was obtained a significant relationship between the increased ratio of CRP / Albumin with a decrease in response to neoadjuvant chemotherapy of CAF in patients with Locally Advanced Breast Cancer.

Keywords: *locally advanced breast cancer, CRP, albumin, CRP/Albumin ratio, response to chemotherapy, breast cancer*

Background

Breast cancer is the most common cancer in women and is the highest cause of death. As many as 2.1 million women in the world suffer from breast cancer each year. In the year 2018, estimated around 627,000 women die the world for cancer of the breast , namely 15% of entire cancer as a cause of death in women[1]. The incidence and number of mortality breast cancer are also increased.[2]

Patients with locally advanced breast cancer (LABC) in particular, require neoadjuvant chemotherapy to reduce tumor size. In the research that is carried out by Oyan et al, on factors prognostic of patients who undergo chemotherapy CAF concluded that age, status

Corresponding Author:
Lintong Darianto Damanik;
First Author; Dr.Soetomo General Hospital Surabaya;
arief.rac.fkunair@gmail.com

gland lymph nodes, the number of focal tumors, and the status of the receptor and multicentric tumor affecting disease-free survival (DFS) either local or remote.

Data at Dr. Soetomo Regional Hospital shows that breast cancer sufferers come in with stage III proportions of 47%. A descriptive-analytic study by Audrina et al in 2011-2013 showed 52% of patients with neoadjuvant chemotherapy experienced a stable disease response. Basic at the top implicated in many studies that discuss the factor- factors that influence the success of chemotherapy

Inflammation regulates tumor behavior at each stage including initiation, promotion, conversion to malignancy, invasion, and metastasis[3]. Increased levels of C-reactive protein (CRP) inflammatory markers are found in various conditions, including malignancy[4]. Increased CRP is a result of their cancer was alone and the inflammatory chronicle that high into the cause of the main occurrence of carcinogenesis. Inflammation causes oxidative stress so it initiates carcinogenesis by activating tumor suppressor gene or modification of DNA-repair protein[5].

Serum albumin is one of the markers most often used to assess a patient's nutritional status. Albumin is produced by the liver and is the main protein in the blood, acting as a key antioxidant, detoxifying, and transporting important nutrients. In patients with locally advanced breast cancer (LABC), the levels of serum albumin often experience a decline, due to malnutrition and response to inflammatory systematically against tumors both suppress the synthesis of albumin.[6]

C-reactive protein and albumin ratio (CAR) was initially used as prognostic value in predicting outcomes in sepsis patients. End- the end of this, the ratio of CRP to albumin promising as a factor prognostic in patients with cancer. Glasgow prognostic score is an indicator of the prognosis of patients with cancer by inflammation which consists of an increase in CRP and a decrease in the concentration of albumin. This marker reflects the systemic inflammatory response in cancer patients and has been reported as a significant prognosis indicator in cancer patients[3]. The CRP to albumin ratio has been used in several types of cancer, one of which is in breast cancer[7].

By due reason in top researchers are very interested to investigate the value of the ratio of CRP compared to albumin in patients with locally advanced breast cancer (LABC) who underwent chemotherapy neoadjuvant based anthracyclines. Some considerations are cases of breast cancer in Surabaya quite a lot and most are found at a locally advanced stage, CAR examination can be done at Dr. Soetomo Regional Hospital and this research has never been done at Dr. Soetomo Regional Hospital before.

Research Method

This study was an observational analytic study with a prospective cohort design. Patients women with LABC who meet the criteria for inclusion and exclusion of studies that the criteria for inclusions are women with LABC which getting chemotherapy neoadjuvant line first CAF / CEF, and agreed to follow research by signing *informed consent*. Criteria for exclusion are patients with recurrent breast cancer, weak general condition; described with Karnofsky score <70%, and patient with a history of Chemotherapy/radiotherapy before.

The study subjects were explained the purpose and benefits of the examination and asked for approval to participate in the study by signing informed consent. Furthermore, the data common subjects such as name, age, type of sex, address, and a number of the phone are recorded. Other data recorded in accordance form and collection of data, includes the calculation of BMI and function physiology of the liver. Do measurements of tumor three days before chemotherapy. The subjects of the study then undergo the examination value of CRP compared to albumin in the blood shortly before chemotherapy neoadjuvant cycle Mining, a, to avoid the effects side of chemotherapy. Subjects will undergo chemotherapy according to the CAF regimen administration procedure. The CAF administration cycle is repeated every 3 weeks until reaching the third cycle. Determination of the dose of CAF based index of the mass of the body (IMT), with a dose of cyclophosphamide 500 mg / m² iv, doxorubicin 50 mg / m² iv, 5FU 500 mg / m². The next will be done measuring the response of clinical and levels of CRP / Albumin patients on a day to 12-14 after undergoing chemotherapy third.

Peng though the data is done using the program SPSS 23.0. Data from variable independent and dependent

form of ordinal data will be tested by using the *chi-square test*, test regression logistic, and *McNemar Test.*

Results

The subjects of the study consisted of 35 women (100%), with the age of majority is the age > 50 years ie 18 patients (51.4%). In the study, it found that the subtype of cancer of breast most are luminal A total 11 patients (31.4%) followed by Luminal B-like (HER-2 positive) as much as 8 patients (22.9 %) with a kind of pathological anatomy most is Invasive carcinoma of no special type (infiltrating ductal carcinoma) Grade III, 16 patients (45.7%). Characteristics of research subjects can be seen in Table 1

Table 1 Characteristics of Research Subjects

Subject Characteristics		**Response (+)**	**Response (+)**	**Total**	**Average**
Age	**<50 years**	**14**	**3**	**17**	**50.31 ± 9.5**
	> 50 years	**14**	**4**	**18**	
Mammae Ca subtype	Basal likes	5	1	6	
	Erb-B2 overexpression	5	0	5	
	Luminal A	5	6	11	
	Luminal B-like (negative HER-2)	6	0	6	

In the study it found that 35 patients had values mean albumin is was 3.4 ± 0.5 g / dl, with the value of the maximum was 4.0 g / dl and a minimum of 1.9 g / dl. On the results of CRP obtained results mean is 0:26 ± 0.2 mg / l with the value of the maximum CRP is 1:20 g / dl and a minimum of 0 .10 g / dl. From the results of the research have obtained ratio CRP / Albumin average is 0 .07 ± 0:06 uL with a value of at least 0:03 uL and a maximum of 0:36 uL. CRP / Albumin Ratios of study subjects are seen in Table 2.

Table 2 CRP / Albumin Ratios in study subjects

	N	**Minimum**	**Maximum**	**The mean**	**Std. Deviation**
	Statistics	**Statistics**	**Statistics**	**Statistics**	**Statistics**
Albumin	35	1.90	4.00	3.4	.50
CRP	35	0.10	1.20	0.26	.20
Ratio	35	0.03	0.36	0.07	.06

CRP ratio value compared to albumin: CRP ratio value compared to albumin is to calculate CRP type divided by albumin type calculation. The results of the examination of CRP and albumin in the blood with the unit uL value will be divided into two categories, namely low with values <0:03 uL and height with a value > 0:03 uL.

Response clinical chemotherapy response to clinical chemotherapy is an evaluation of changes in the size of the tumors were measured by an objectively thorough examination of the physical, divided into four categories, namely: progressive disease, stable disease, partial response, and complete response. In the study, it found that most large patients experienced a partial

response which is as many as 22 patients (64.7%).

In research, it then does test the relationship of variables independent and dependent form of the data ordinal and nominal. From the research data, it was found that the majority were responses (+) having a low CRP / Albumin ratio.

Table 3 Cross Tabulation of CRP / Albumin Ratios with Chemotherapy Response

		Chemo Response		Total
		Response (+)	Response (-)	
CRP / ALB category	Low	27	5	32
	High	1	2	3
Total		28	7	35

The relationship between the ratio of CRP / Albumin in response to clinical patient cancer breast up locally tested by using the *chi-square test* and coefficient contingency then obtained the result that there is a relationship that significant between the ratio CRP / Albumin in response to clinical patient cancer breast up locally with the value p-value = 0.004 ($p < 0.05$) which means that there is a significant relationship as shown in Table 6 and Table 7

Table 4 Chi-Square Test CRP / Albumin ratio with clinical response of locally advanced breast cancer patients

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	11,292 a	2	.004
Likelihood Ratio	12,543	2	.002
Linear-by-Linear Association	4,928	1	.026
N of Valid Cases	35		

Table 5 Test Contingency Coefficient ratio CRP / Albumin in response to clinical patients of cancer of breast more local

		Value	Asymptotic Standard Error a	Approximate T b	Approximate Significance
Nominal by Nominal	Contingency Coefficient	.494			.004
Ordinal by Ordinal	Gamma	-.591	267	1,950	.051
	Spearman Correlation	-.369	.178	-2,280	.029 c
Interval by Interval	Pearson's R.	-381	.165	-2,365	.024 c
N of Valid Cases		35			

Discussion

In this study, it was found that an increase in CRP, a decrease in albumin (high CAR) decreased the response of neoadjuvant therapy from breast cancer. In studies, an increase in CRP correlates significantly with an increase in the stage, size, and extent of the tumor, and metastasis[8].

Chronic inflammation is known to play a role in increasing carcinogenesis, which is associated with processes that contribute to the onset or development of cancer. Rapid tumor growth can cause an immune response, and many inflammatory factors are released. Inflammation can contribute to tumorigenesis by supplying bioactive molecules to the tumor microenvironment, including growth factors that cause proliferation; survival factors that reduce cell death; proangiogenic factors and extracellular matrix modifying enzymes that stimulate angiogenesis, invasion, and metastasis; and inductive signals that facilitate the epithelial to mesenchymal transition and other effects. Specifically, chronic inflammation can increase the risk of BC through activating redox transcription factors, increasing local estrogen production, and inducing angiogenesis. This in addition to increasing the stage of the disease also decreases the effectiveness of the chemotherapy given.[9] Chronic inflammation not only changes the tumor microenvironment by dissolved mediators but also through the recruitment of differentiated cells into tumors and their microenvironment. Recent studies have shown that tumor carcinogenesis is characterized by important differences in the genetic and epigenetic transformation of the epithelium, stroma, structure of blood vessels, and immune cells. Thus, inflammation may not only be important in the initiation of DNA damage but through increased release of cytokines, reactive oxygen species, and relative hypoxia, it can also cause an increased cycle of epigenetic changes.[10]

Serum albumin has been used to assess disease severity, disease progression, and prognosis. Albumin is the main protective element that can stabilize DNA replication and cell growth, which can fight carcinogenesis by aflatoxin and nitrosamines. Also, several studies recommend that high concentrations of albumin can inhibit the growth of various tumor cells. Albumin formation can be suppressed by inflammation and malnutrition, which are pathological factors of many cancers. Cytokines, such as TNF and IL-6, are produced by the inflammatory response, which can reduce albumin synthesis by smaller cells. Previous studies confirm that low levels are associated with poor prognosis in some malignancies[11].

The relationship between low albumin and decreased neoadjuvant chemotherapy response is not much related to the role of albumin as a vehicle for chemotherapy drugs. The albumin binding with cyclophosphamide and 5-fluorouracil is very low, so albumin has no role in bringing chemotherapy drugs to the cancerous area. This shows that the role of albumin, in this case, is more general.[12, 13]

Several other studies have also evaluated the relationship between serum albumin levels and CRP ratio with the survival of locally advanced breast cancer patients with anthracycline-based neoadjuvant chemotherapy, as a result, that a higher CRP-albumin serum ratio is an indicator for worse survival and more therapeutic response. bad. Elevated serum CRP levels detected before treatment can indicate tumor aggressiveness and may be related to treatment resistance and adverse outcomes in patients with breast cancer[14].

Six studies consisting of 2904 patients also reported results to see an association with disease-free survivability (DFS), and the results collected showed that increased CAR was associated with poor DFS[14]. Thus, CAR can be used as a parameter to see neoadjuvant chemotherapy responses in breast cancer patients.

Conclusion

There is a significant relationship between the increase in the ratio of CRP / Albumin with a decrease in response to chemotherapy neoadjuvant CAF in patients with *Locally Advanced Breast Cancer*.

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